Supporting information

Synthesis of trisubstituted imidazoles by Palladium-catalysed cyclisation of *O*-pentafluorobenzoylamidoximes: application to amino acid mimetics with a C-terminal imidazole

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General Experimental Methods. Melting points were taken on an electrothermal apparatus and are uncorrected. NMR experiments were performed at 500 MHz or 300 MHz for ^1H NMR and at 75 MHz for ^{13}C NMR with internal standard TMS (^1H NMR) and the solvent signal (^{13}C NMR). Optical rotations were obtained on a digital polarimeter and data are reported as $[\alpha]_D^{25}$ (concentration g/100 mL, solvent). All reactions were carried out in oven-dried glassware under an argon atmosphere. THF was distilled from Na/Ph₂CO, while CH₂Cl₂, Et₃N, and benzene were distilled from CaH₂. Oximes **2a**³, **2b**⁴, **8a-c**⁵ and hydroxamoyl chloride **3c**⁶ were prepared by the literature methods.

General Procedure A: Preparation of amidoximes. To a solution of the oxime (1.0 equiv) in dry DMF (25 mL), was added N-chlorosuccinimide (1.01 equiv) in portions. The reaction mixture was heated to 50-70 °C with stirring for 2 h, and then cooled to rt. A solution of *N*-allyl benzyl amine¹ (1.2 equiv) in DMF (5mL) was added and stirring was continued for 2-4 h, as monitored by TLC. The mixture was cooled to rt, water was added, and the mixture extracted with ethyl acetate (x3). The combined organic extracts were washed with water, NaHCO₃ soln (aq.), brine, dried (MgSO₄), evaporated in vacuo, and the crude residue purified by flash column chromatography.

General Procedure B: Preparation of *O*-pentafluorobenzoyl amidoximes. To a solution of the amidoxime (1 equiv) and TEA (1.2 equiv) in dry CH₂Cl₂ (20mL) at 0 °C, was added C₆F₅COCl (1.2 equiv) in CH₂Cl₂ (5 ml) and the mixture was stirred for 2 h at the same temperature. Water was added and the mixture extracted with CH₂Cl₂ (x3). The combined organic extracts were washed with water, NaHCO₃ soln (aq.), brine, dried (MgSO₄), evaporated in vacuo, and the crude residue purified by flash column chromatography.

General procedure C: Amino-Heck Preparation of imidazoles. Pd(PPh₃)₄ (0.01 equiv) was added to a solution of the *O*-pentafluorobenzoyl amidoxime (1 equiv) and TEA (5 equiv) in dry DMF (0.05 M) under argon atmosphere at rt. The reaction mixture was warmed to 80 °C and stirring was continued for 30 min to 1h (as monitored by TLC). The

reaction mixture was cooled to rt, quenched by adding water and extracted with Et₂O (x3). The combined extracts were washed with water, brine (x2), dried over anhydrous MgSO₄, evaporated in vacuo, and the residue purified by flash column chromatography.

Preparation of (*E*)-4a.

(*E/Z*)-**2a** (1:1) (400 mg, 2.96 mmol), NCS (400 mg, 2.99 mmol) and *N*-allyl benzyl amine (849 mg, 3.55 mmol) in dry DMF (25 mL) were reacted according to general method A and the residue purified by flash column chromatography (PE/EA = 9:1 then 4:1) to give 525 mg (63%) of (*E*)-**4a** as a yellow crystalline solid. ¹H NMR (500 MHz) δ 3.72 (d, *J* = 5.5 Hz, 2H, NCH₂CH), 3.98 (s, 2H, PhCH₂CN), 4.32 (s, 2H, NCH₂Ph), 5.09 (dd, *J* = 22 Hz, 10 Hz, 2H, CHCH₂), 5.67-5.75 (m, 1H, NCH₂CHCH₂), 7.13 (d, *J* = 8 Hz, 2H, Ar), 7.20-7.23 (m, 2H, Ar), 7.26-7.34 (m, 6H, Ar); ¹³C NMR (75 MHz) δ 30.4, 49.9, 50.4, 116.8, 126.4, 126.9, 127.1, 128.3, 128.5, 128.6, 133.5, 136.2, 138.3, 159.1. HRMS (ES⁺) calcd for C₁₈H₂₁N₂O [MH]⁺: 281.1654, found. 281.2135.

Preparation of (*E*)-4b.

(a) (*E/Z*)-**2b** (3:2) (235 mg, 1.57 mmol), NCS (211 mg, 1.59 mmol) and *N*-allyl benzyl amine (276 mg, 1.88 mmol) in dry DMF (25 mL) were reacted according to general method A and the residue purified by flash column chromatography (PE/EA = 9:1 then 4:1) to give 370 mg (61%) of (*E*)-**4b** as a cream solid. ¹H NMR (500 MHz) δ 2.80-2.94 (m, 4H, CH₂CH₂), 3.73 (d, *J* = 5.5 Hz, 2H, NCH₂CH), 4.31 (s, 2H, NCH₂Ph), 5.08-5.16 (m, 2H, CHCH₂), 5.74-5.82 (m, 1H, NCH₂CHCH₂), 7.20 (t, *J* = 7.5 Hz, 4H, Ar), 7.23-7.33 (m, 6H, Ar); ¹³C NMR (75 MHz) δ 27.0, 32.6, 49.9, 50.5, 116.8, 126.2, 127.0, 127.2, 128.4, 128.4, 128.5, 133.8, 138.4, 141.4, 160.8. HRMS (ES⁺) calcd for C₁₉H₂₃N₂O [MH]⁺: 295.1810, found 295.1694.

(b) (*E/Z*)-**2b** (3:2) (1.87 g, 12.61 mmol), and NCS (1.68 mg, 12.61 mmol) in dry DMF (25 mL) were reacted according to the modified general method A. Work up as for **4b** gave 2.0 g (87%) of (*E*)-**3b** as a yellow oily solid. ¹H NMR (300 MHz) δ 2.77-2.82 (m, 2H, PhCH₂), 2.94-2.99 (m, 2H, CH₂), 7.18-7.32 (m, 5H, Ar). A solution of (*E*)-**3b** (50 mg, 0.27 mmol) and *N*-allyl benzyl amine (40 mg, 0.27 mmol) in dry DMF

(20 mL) was stirred at 50-70° C for 2 h. Workup as described in general procedure A, followed by purification by flash column chromatography (PE/EA = 2:1) gave 56 mg (66%) of (*E*)-**4b** as a cream coloured solid. ¹H NMR as given above.

Preparation of (*E/Z*)-**4c**

A solution of (*E/Z*)-**3c** (6:5) (502 mg, 4.0 mmol) and *N*-allyl benzyl amine (586 mg, 4.0 mmol) in dry DMF (20 mL) was stirred at 50-70° C for 2 h. Workup as described in general procedure A, followed by purification by flash column chromatography (PE/EA = 2:1) gave 748 mg (75%) of (*EZ*)-**4c** (6:5) as a yellow solid. ¹H NMR mixture of isomers (300 MHz) δ 3.63 (d, *J* = 6 Hz, 2H, NCH₂CHCH₂, major), 3.73 (s, 3H, CH₃, minor), 3.78 (d, *J* = 7 Hz, 2H, NCH₂CHCH₂, minor), 3.89 (s, 3H, CH₃, major), 4.26 (s, 2H, NCH₂Ph, major), 4.44 (s, 2H, NCH₂Ph, minor), 5.09-5.21 (m, 2H, CHCH₂, minor & major), 5.69-5.93 (m, 1H, CHCH₂, minor & major), 7.23-7.35 (m, 5H, Ar, minor & major), 7.49 (bs, 1H, C=NOH, major), 9.16 (bs, 1H, C=NOH, minor); ¹³C NMR mixture (75 MHz) δ 49.7 (minor), 50.8 (minor), 52.4 (minor), 52.7 (minor), 52.6 (major), 53.5 (major), 117.9 (major), 118.3, 127.2, 127.5, 127.8, 128.0, 128.4, 128.5, 132.1 (minor), 134.4 (major), 136.3, 137.9, 146.4 (major), 154.4 (minor), 162.5 (major), 162.7 (minor); HRMS (ES⁺) calcd for C₁₃H₁₇N₂O₃ 249.1239 [MH]⁺, found: 249.1142.

Preparation of (*E*)-**5a**

A solution of (*E*)-**4a** (461 mg, 1.64 mmol), TEA (300 µL, 2.14 mmol), and C₆F₅COCl (492 mg, 2.14 mmol) in dry DCM (30 mL) was reacted as described in general procedure B, and the crude product purified by flash column chromatography (PE/EA = 49:1) to give 650 mg (83%) of (*E*)-**5a** as a colorless oil. ¹H NMR(500 MHz) δ 3.87 (d, *J* = 5 Hz, 2H, NCH₂CH), 3.98 (s, 2H, PhCH₂CN), 4.50 (s, 2H, NCH₂Ph), 5.16 (dd, *J* = 24 Hz, 10 Hz, 2H, CHCH₂), 5.73-5.81 (m, 1H, CHCH₂), 7.19 (t, *J* = 8 Hz, 4H, Ar), 7.27 (t, *J* = 7 Hz, 2H, Ar), 7.32 (t, *J* = 7 Hz, 4H, Ar); ¹³C NMR (75 MHz) δ 32.2, 50.0, 50.5, 107.9 (m), 117.6, 126.9, 127.3, 127.4, 127.7, 128.6, 129.1, 132.5, 134.5, 135.7-139.5 (m), 137.0, 140.9-144.9 (m), 143.2-147.1 (m), 156.9, 164.9. Anal. Calcd for C₂₅H₁₉F₅N₂O₂: C, 63.29; H, 4.04; N, 5.90. Found: C, 63.44; H, 4.08; N, 5.68.

Preparation of (*E*)-**5b**

A solution of (*E*)-**4b** (273 mg, 0.93 mmol), TEA (150 μ L, 0.99 mmol) and $\text{C}_6\text{F}_5\text{COCl}$ (229 mg, 0.99 mmol) in dry DCM (30 mL) was reacted as described in general procedure B, and the crude product purified by flash column chromatography (PE/EA = 49:1) to give 393 mg (87%) of (*E*)-**5b** as a white solid. ^1H NMR (500 MHz) δ 2.81-2.91 (m, 4H, CH_2CH_2), 3.83 (d, $J = 5.5$ Hz, 2H, NCH_2CH), 4.44 (s, 2H, NCH_2Ph), 5.12-5.19 (m, 2H, CHCH_2), 5.76-5.83 (m, 1H, CHCH_2), 7.11 (d, $J = 7.5$ Hz, 2H, Ar), 7.18-7.29 (m, 6H, Ar), 7.34 (t, 2H, $J = 7$ Hz, Ar); ^{13}C NMR (75 MHz) δ 28.4, 32.8, 50.1, 50.5, 107.0 (m), 117.5, 126.5, 127.3, 128.1, 128.5, 128.6, 132.6, 135.7-139.5, (m), 137.1, 139.8, 140.9-144.9 (m), 143.2-147.1 (m), 156.8, 166.7. Anal Calcd for $\text{C}_{26}\text{H}_{21}\text{F}_5\text{N}_2\text{O}_2$: C, 63.93; H, 4.33; N, 5.74. Found: C, 64.07; H, 4.49; N, 5.70. HRMS (ES^+) calcd for $\text{C}_{26}\text{H}_{22}\text{F}_5\text{N}_2\text{O}_2$: 489.1601 $[\text{MH}]^+$, found: 489.1610.

Preparation of (*EZ*)-**5c**

A solution of **4c** (594 mg, 2.39 mmol), TEA (420 μ L, 2.75 mmol) and $\text{C}_6\text{F}_5\text{COCl}$ (634 mg, 2.75 mmol) in dry DCM (30 mL) was reacted as described in general procedure B, and the crude product purified by flash column chromatography (PE/EA = 2:1) to give 835 mg (88%) of (*EZ*)-**5c** (4:1 by ^1H NMR) as a yellow solid. ^1H NMR mixture (500 MHz) δ 3.85-3.99 (m, 5H, NCH_2CH , CH_3 , minor & major), 4.42 (s, 2H, NCH_2Ph , minor), 4.53 (s, 2H, NCH_2Ph , major), 5.16-5.28 (m, 2H, CHCH_2 , minor & major), 5.75-5.88 (m, 1H, CHCH_2 , minor & major), 7.18-7.44 (m, 5H, Ar, minor & major); ^{13}C NMR mixture (75 MHz) δ 49.7, 50.8, 52.9, 53.6, 54.0, 54.3, 106.8 (m), 119.2, 119.3, 126.7, 127.4, 127.9, 128.1, 128.5, 128.7, 131.1, 132.4, 135.1, 135.5-147.3 (m, 3xC both isomers), 136.2, 151.5, 159.4, [155.4, 156.1, 160.1, 161.4. HRMS (ES^+) calcd for $\text{C}_{20}\text{H}_{16}\text{F}_5\text{N}_2\text{O}_4$ $[\text{MH}]^+$ 443.1030, found: 443.1023.

Preparation of **6a**

A mixture of (*E*)-**5a** (169 mg, 0.36 mmol), TEA (300 μ L, 1.78 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (41 mg, 0.035 mmol) in dry DMF (7 mL) was treated as described in general procedure C with heating at 80 $^\circ\text{C}$ for 30 min. The residue was purified by flash column chromatography (PE/EA = 3:2 then 1:9) to give 62 mg (65%) of **6a** as a yellow oil. ^1H

NMR (500 MHz) δ 2.22 (s, 3H, CH₃), 4.02 (s, 2H, PhCH₂), 4.80 (s, 2H, NCH₂Ph), 6.52 (s, 1H, CHN), 6.92 (dd, J = 6 Hz, 1Hz, 2H, Ar), 7.14 (d, J = 7.5 Hz, 2H, Ar), 7.19 (t, J = 7.5 Hz, 1H, Ar), 7.27 (m, 5H, Ar); ¹³C NMR (75 MHz) δ 13.6, 33.7, 49.3, 116.7, 126.5, 126.7, 127.7, 128.2, 128.6, 128.7, 136.3, 136.4, 137.3, 145.8. HRMS (ES⁺) calcd for C₁₈H₁₉N₂ [MH]⁺ 263.1548, found: 263.1436.

Preparation of 6b

A mixture of (*E*)-**5b** (151 mg, 0.31 mmol), TEA (230 μ L, 1.55 mmol), and Pd(PPh₃)₄ (36 mg, 0.031 mmol) in dry DMF (6 mL) was treated as described in general procedure C with heating at 80 °C for 30 min. The residue was purified by flash column chromatography (PE/EA = 3:2 then 1:9) to give 53 mg (62%) of **6b** as a yellow oil. ¹H NMR (500 MHz) δ 2.23 (s, 3H, CH₃), 2.85-3.01 (m, 4H, CH₂CH₂), 4.80 (s, 2H, NCH₂Ph), 6.50 (s, 1H, CHN), 7.00 (d, J = 7 Hz, 2H, Ar), 7.11 (d, J = 7.5 Hz, 2H, Ar), 7.19 (t, J = 7.5 Hz, 1H, Ar), 7.26-7.33 (m, 5H, Ar); ¹³C NMR (75 MHz) δ 13.5, 29.1, 34.7, 49.1, 116.1, 126.2, 126.7, 127.9, 128.4, 128.5, 128.9, 136.3, 136.6, 137.3, 141.2, 147.0. HRMS (ES⁺) calcd for C₁₉H₂₁N₂ [MH]⁺ 277.1705, found: 277.1605.

Preparation of 6c

A mixture of (*E/Z*)-**5c** (4:1, 226 mg, 0.51 mmol), TEA (400 μ L, 2.55 mmol) and Pd(PPh₃)₄ (59mg, 0.051 mmol) in dry DMF (9 mL) was treated as described in general procedure C with heating at 80 °C for 3 h. The residue was purified by flash column chromatography (PE/EA = 3:2) to give (34mg, 30%) of **6c** as a yellow oil. ¹H NMR (500 MHz) δ 2.18 (s, 3H, CH₃), 3.84 (s, 3H, OCH₃), 5.51 (s, 2H, CH₂Ph), 6.74 (s, 1H, CHN), 7.11 (d, J = 7 Hz, 2H, Ar), 7.19-7.28 (m, 3H, Ar); ¹³C NMR (75 MHz) δ 13.7, 51.3, 52.2, 122.5, 127.4, 128.0, 128.8, 134.8, 136.4, 139.1, 159.4. HRMS (ES⁺) calcd for C₁₃H₁₅N₂O₂ [MH]⁺ 231.1134, found: 231.1181.

Preparation of (*E,S*)-11a

A mixture of (*E/Z*)-**8a** (2:1, 400 mg, 1.52 mmol), NCS (204 mg, 1.53 mmol) and N-allyl benzyl amine (268 mg, 1.82 mmol) in dry DMF (10 mL) were reacted according to general method A and the crude residue (isomer ratio 3:1 by ¹H NMR) was subjected to

flash column chromatography (PE/EA = 9:1 then 17:3) to give 300 mg of (*E/Z*)-**10a** as a slightly impure yellow foam that was not purified further (isomer ratio 5:2 by ^1H NMR). HRMS (ES^+) calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ $[\text{MH}]^+$ 410.2444, found: 410.2122. A sample of (*E/Z*)-**10a** (285 mg), TEA (90 μL , 0.60 mmol) and $\text{C}_6\text{F}_5\text{COCl}$ (138 mg, 0.60 mmol) in dry DCM (15 mL) was reacted as described in general procedure B, and the crude product purified by flash column chromatography (PE/EA = 97/3) to give 210 mg (61%) of (*E*)-**11a** as a colorless oil. ^1H NMR (500 MHz) δ 1.41 (s, 9H, *t*-Bu), 3.07-3.15 (m, 2H, PhCH_2CH), 3.70 (dd, $J = 16.5$ Hz, 5 Hz, 1H, $\text{NCH}_\text{A}\text{CH}$), 3.95 (dd, $J = 16.5$ Hz, 5 Hz, 1H, $\text{NCH}_\text{B}\text{CH}$), 4.35 (d, $J = 16$ Hz, 1H, $\text{NCH}_\text{A}\text{Ph}$), 4.45 (d, $J = 16$ Hz, 1H, $\text{NCH}_\text{B}\text{Ph}$), 4.93 (dd, $J = 17$ Hz, 8 Hz, 1H, CH), 5.10 (m, 2H, CHCH_2), 5.49 (d, $J = 10$ Hz, 1H, NH), 5.60-5.67 (m, 1H, CHCH_2), 7.03-7.07 (m, 4H, Ar), 7.21-7.26 (m, 6H, Ar); ^{13}C NMR (75 MHz) δ 28.2, 39.1, 51.2, 51.5, 51.8, 80.1, 108.0 (m), 117.7, 127.0, 127.2, 127.3, 128.4, 128.6, 129.2, 132.6, 135.7-139.7 (m), 136.4, 136.7, 141.2-144.7 (m), 142.9-146.4 (m), 155.1, 158.0, 165.2; $[\alpha]_\text{D}^{20}$ -1.4 (*c* 1.3 CHCl_3); HRMS (ES^+) calcd for $\text{C}_{31}\text{H}_{31}\text{F}_5\text{N}_3\text{O}_4$ $[\text{MH}]^+$ 604.2235, found: 604.2239.

Preparation of (*E,S*)-**11b**

A mixture of (*E/Z*)-**8b** (3:1, 400 mg, 2.12 mmol), NCS (286 mg, 2.14 mmol) and *N*-allyl benzyl amine (312 mg, 2.12 mmol) in dry DMF (10 mL) were reacted according to general method A and the crude residue (isomer ratio 8:3 by ^1H NMR) was subjected to flash column chromatography (PE/EA = 9:1 then 17:3) to give a slightly impure sample of **10b** as a single isomer 210 mg (30%) which was not purified further. HRMS (ES^+) calcd for $\text{C}_{18}\text{H}_{28}\text{N}_3\text{O}_3$ $[\text{MH}]^+$ 334.2131, found: 334.2021. A sample of (*E/Z*)-**10b** (170 mg), TEA (80 μL , 0.54 mmol) and $\text{C}_6\text{F}_5\text{COCl}$ (123 mg, 0.54 mmol) in dry DCM (15 mL), was reacted as described in general procedure B, and the crude product purified by flash column chromatography (PE/EA = 97:3) to give 170 mg (63%) of (*E*)-**11b** as a viscous colorless oil. ^1H NMR (500 MHz) δ 1.41 (d, $J = 7.5$ Hz, CH_3CH), 1.45 (s, *t*-Bu), 3.77 (dd, $J = 17$ Hz, 5 Hz, 1H, NCH_2CH), 4.33 (m, 1H, NCH_2CH), 4.38 (d, $J = 16.5$ Hz, 1H, $\text{NCH}_\text{A}\text{Ph}$), 4.75-4.81 (m, 2H, $\text{NCH}_\text{B}\text{Ph}$, CH_3CH), 5.18-5.22 (m, 2H, CHCH_2), 5.36 (d, $J = 9$ Hz, 1H, NH), 5.81-5.89 (m, 1H, CHCH_2), 7.22-7.32 (m, 5H, Ar); ^{13}C NMR (75 MHz) δ 18.6, 28.2, 45.2, 51.8, 52.2, 80.0, 108.0, 117.2, 127.1, 127.2, 128.5, 132.9, 135.7-

139.4 (m), 137.0, 141.0-144.7 (m), 142.8-146.3 (m), 155.2, 157.2, 166.8; $[\alpha]_D^{20} +33.2$ (c 1.0 CHCl₃); HRMS (ES⁺) calcd for C₂₅H₂₇F₅N₃O₄ [MH]⁺ 528.1922, found: 528.1944.

Preparation of (*E,S*)-11c

A mixture of (*E/Z*)-8c (3:2, 600 mg, 2.79 mmol), NCS (372 mg, 2.79 mmol) and N-allyl benzyl amine (414 mg, 2.81 mmol) in dry DMF (10 mL) were reacted according to general method A and the crude residue (isomer ratio 11:1 by ¹H NMR) was subjected to flash column chromatography (PE/EA = 9:1 then 17:3) to give 180 mg (20%) of (*E/Z*)-10c as a slightly impure yellow gum (isomer ratio 5:1 by ¹H NMR). Selected data for major isomer: HRMS (ES⁺) calcd for C₂₁H₃₄N₃O₃ [MH]⁺ 376.2600, found: 376.2558. A sample of (*E/Z*)-10c (150 mg), TEA (64 μL, 0.46 mmol) and C₆F₅COCl (106 mg, 0.46 mmol) in dry DCM (15 mL) was reacted as described in general procedure B, and the crude product purified by flash column chromatography (PE/EA = 97/3) to give 40% of recovered starting material 10c and 75 mg (31%) of (*E*)-11c as a colorless oil. ¹H NMR (500 MHz) δ 0.72 (d, *J* = 6.5 Hz, 3H, CH₃), 0.86 (d, *J* = 6.5 Hz, 3H, CH₃), 0.93-1.01 (m, 1H, (CH₃)₂CH), 1.45 (s, *t*-Bu), 1.59-1.65 (m, 1H, CHCH₂CH), 1.87-1.93 (m, 1H, CHCH₂CH), 3.80 (dd, *J* = 16.5 Hz, 5 Hz, 1H, NCH_ACH), 4.28 (dd, 1H, *J* = 17 Hz, 4 Hz, NCH_BCH), 4.41 (d, *J* = 16.5 Hz, 1H, NCH_APh), 4.61-4.72 (m, 1H, CH), 4.75 (d, *J* = 16.5 Hz, 1H, NCH_BPh), 5.17-5.21 (m, 2H, CHCH₂), 5.25 (d, *J* = 9.5 Hz, 1H, NH), 5.81-5.88 (m, 1H, CHCH₂), 7.20-7.32 (m, 5 H, Ar); ¹³C NMR (75 MHz) δ 21.2, 23.2, 25.1, 28.2, 41.3, 48.3, 51.8, 52.1, 79.9, 108.0 (m), 117.5, 127.1, 127.2, 128.5, 132.7, 135.6-139.5 (m), 137.0, 140.9-144.9 (m), 142.5-146.4 (m), 155.5, 157.2, 166.8; $[\alpha]_D^{20} + 59.8$ (c 2.0 CHCl₃); HRMS (ES⁺) calcd for C₂₈H₃₂F₅N₃NaO₄ [M]⁺[Na] 592.2211, found: 592.1835.

Preparation of (*S*)-12a

A mixture of (*E*)-11a (100 mg, 0.17 mmol), TEA (120 μL, 0.83 mmol) and Pd(PPh₃)₄ (19 mg, 0.017 mmol) in dry DMF (4 mL) was treated as described in general procedure C with heating at 80 °C for 30 min. The residue was purified by flash column chromatography (PE/EA = 3:2 then 1:4) to give 45 mg (70%) of 12a as a yellow solid. ¹H NMR (500 MHz) δ 1.36 (s, 9H, *t*-Bu), 2.20 (s, 3H, CH₃), 3.12-3.22 (m, 2H, PhCH₂), 4.67 (m, 2H, NCH₂Ph), 4.95 (m, 1H, CH), 5.44 (bd, *J* = 8.5 Hz, 1H, NH), 6.35 (bs, 1H,

CHN), 6.88 (m, 2H, Ar), 7.02 (d, $J = 5.4$ Hz, 2H, Ar), 7.19-7.23 (m, 6H, Ar); ^{13}C NMR (75 MHz) δ 13.6, 28.3, 42.0, 48.0, 48.9, 79.4, 115.9, 126.5, 127.2, 127.8, 129.3, 128.7, 129.5, 136.3, 136.7, 137.4, 147.0, 155.0; $[\alpha]_{\text{D}}^{20}$ -8.3 (c 1.0 CHCl_3); HRMS (ES^+) calcd for $\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_2$ $[\text{MH}]^+$ 392.2338, found: 392.2330.

Preparation of (S)-12b

A mixture of (*E*)-**11b** (110 mg, 0.21 mmol), TEA (145 μL , 1.09 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (24 mg, 0.021 mmol) in dry DMF (6 mL) was treated as described in general procedure C with heating at 80 $^\circ\text{C}$ for 1 h. The residue was purified by flash column chromatography (EA/PE = 7:3) to give 42 mg (68%) of **12b** as a yellow solid. ^1H NMR (500 MHz) δ 1.39 (s, 9H, *t*-Bu), 1.43 (d, $J = 7$ Hz, 3H, CH_3CH), 2.19 (d, $J = 1$ Hz, 3H, CH_3), 4.88-4.94 (m, 1H, CH_3CH), 5.08 (d, $J = 16$ Hz, 1H, $\text{NCH}_\text{A}\text{Ph}$), 5.16 (d, $J = 16$ Hz, 1H, $\text{NCH}_\text{B}\text{Ph}$), 5.27 (bd, $J = 8.5$ Hz, 1H, NH), 6.52 (s, 1H, CHN), 7.10 (d, $J = 7.5$ Hz, 2H, Ar), 7.28-7.33 (m, 3H, Ar); ^{13}C NMR (75 MHz) δ 13.5, 20.9, 28.3, 41.9, 49.1, 79.4, 116.5, 126.8, 127.8, 128.8, 136.4, 136.7, 148.2, 154.9; $[\alpha]_{\text{D}}^{20}$ -72.4 (c 1.0 CHCl_3); HRMS (ES^+) calcd for $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_2$ $[\text{MH}]^+$ 316.2025, found: 316.2063.

Preparation of (S)-12c

A mixture of (*E*)-**11c** (51 mg, 0.09 mmol), triethylamine (62 μL , 0.44 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (10 mg, 0.009 mmol) in dry DMF (6 mL) was treated as described in general procedure C with heating at 80 $^\circ\text{C}$ for 1 h. The residue was purified by flash column chromatography (PE/EA = 7:3 then 3:7) to give 18 mg (56%) of **12c** as a thick colorless oil. ^1H NMR (500 MHz) δ 0.78 (m, 6H, 2x CH_3), 1.38 (s, 9H, *t*-Bu), 1.52-1.56 (m, 2H, CH_2CH), 1.81 (t, $J = 14.5$ Hz, 1H, CH_2CH), 2.19 (d, $J = 1.5$ Hz, 3H, CH_3), 4.83-4.88 (m, 1H, CH), 5.04-5.25 (m, 3H, NH, NCH_2), 6.52 (s, 1H, CH_3CCHN), 7.13 (d, $J = 10$ Hz, 2H, Ar), 7.27-7.35 (m, 3H, Ar); ^{13}C NMR (75 MHz) δ 13.6, 21.8, 22.8, 24.60, 28.3, 43.8, 44.0, 49.1, 79.3, 116.3, 127.0, 127.8, 128.8, 136.5, 136.9, 148.4, 155.2; $[\alpha]_{\text{D}}^{20}$ -54.3 (c 1.0 CHCl_3); HRMS (ES^+) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_3\text{O}_2$ $[\text{MH}]^+$ 358.2495, found: 358.2596.

Preparation of **13**

Compound **12a** (20 mg, 0.05 mmol) was treated with 1 N aq. HCl (1 mL) in EtOAc (3 mL) at rt with stirring for 3 h. The progress of the reaction was monitored by TLC. The solvent was evaporated in vacuo, MeOH was added (x2), and solvent evaporated. This was repeated two times. The crude product was dried in vacuo and used in the subsequent step without further purification. (*S*)-N-Boc-alanine (9.7 mg, 0.05 mmol) was added to the crude amine (15 mg, 0.051 mmol), EDCI (10 mg, 0.05 mmol), HOBT (14 mg, 0.10 mmol) and DIPEA (0.18 μ L) in dry DMF (6 mL) and the mixture stirred at rt for 16h. Water (2 mL) and EtOAc (4 mL) were added, the organic phase separated, and the aq. phase extracted with EtOAc (x3). The combined organic fractions were washed with H₂O (x2), NaHCO₃, brine, dried (MgSO₄) and evaporated in vacuo. The residue (a single diastereoisomer by ¹H NMR) was purified by flash column chromatography (PE/EtOAc = 1:1 then 7:3) to give **13** (12mg, 52%) as a clear oil. ¹H NMR (500 MHz) δ 1.20 (d, *J* = 7.5 Hz, 1H, CH₃CH), 1.41 (s, 9H, *t*-Bu), 2.19 (s, 3H, CH₃), 3.11-3.15 (m, 1H, PhCH_ACH), 3.20 (dd, *J* = 13.5 Hz, 7 Hz, 1H, PhCH_BCH), 4.08 (bs, 1H, CH₃CH), 4.66-4.75 (m, 3H, NCH, NH), 4.89 (bm, 1H, NH), 5.26 (dd, *J* = 15.5 Hz, 8.5 Hz, 1H, CH₂CH), 6.37 (s, 1H, CHN), 6.88 (t, *J* = 3.5 Hz, 2H, Ar), 7.01 (m, 3H, Ar), 7.19-7.27 (m, 5H, Ar); ¹³C NMR (75 MHz) δ 13.4, 18.3, 28.2, 41.2, 46.4, 48.9, 50.2, 80.0, 116.2, 126.6, 127.0, 127.8, 128.3, 128.8, 129.4, 136.2, 136.6, 137.1, 146.3, 155.1, 171.7.

References

1. Mustapha, K; Michel P, C; Marie, J. S. *Bull. Chim. Soc. Fr.* **1981**, 11-12, 449.
2. Tsutsui, H; Narasaka, K. *Chem. Lett.* **1999**, 45.
3. Lam, P. Y. S; Adams, J. J; Clark, C. G; Calhoun, W. J; Luetttgen, J. M; Knabb, R. M; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2003**, 13, 1795.
4. Boucher, J-L; Delaforge, M; Mansuy, D. *Biochemistry* **1994**, 33, 7811.
5. Chung, Y. J; Ryu, E. J; Keum, G; Kim, H. *Bioorg. Med. Chem.* **1996**, 4, 209.
6. Abbott, S. D; Lane-Bell, P; Sidhu, K. P. S; Vederas, J. C. *J. Am. Chem. Soc.* **1994**, 116, 6513.